REMARKS

I. Examiner Interview

Applicant thanks Examiner Popa and Primary Examiner Woitach for the Examiner Interview of June 5, 2007.

II. The claims

Pursuant to this paper, claims 1-40 are pending. Claims 1-16 are presently withdrawn as a result of being deemed to be directed to a non-elected inventions and claims 21, 23, 26, 28, 31 and 33-35 are presently withdrawn as being drawn to non-elected species.

Claims 18 and 29 have amended herein. Support for said amendments is found in originally filed claims 18 and 29, respectively.

New claims 39 and 40 have been added. Support for new claims 39 and 40 is found, for example, in the originally filed specification at page 3, l. 28-29 and in originally filed claim 36.

Elected claims 17-20, 22, 24, 25, 27, 29, 30, 32 and 36-38 were examined on the merits and were rejected in the non-final Office Action mailed May 2, 2007, but were previously found to be free of the prior art in the Office Action mailed February 13, 2006 (see ¶7 thereof).

No new matter has been added by any of the amendments made herein.

III. Claim rejections under 35 U.S.C. §112 – enablement requirement

Claims 17-20, 22, 24, 25, 27, 29, 30, 32 and 36-38 were rejected for alleged lack of enablement under 35 U.S.C. §112, paragraph 1. (Present Office Action, ¶¶3 and 4.) The main and minor aspects of the Examiner's rejections are discussed and responded to below.

III(A.) The Examiner first asserted what is regarded as the "main problem" in connection with enablement, as follows:

> Although it is true that gene silencing is well documented in plants and can be achieved in animals in certain situations, the main problem is that the instant claims require a cell expressing a repressible promoter operably linked to a site specific recombinase and a gene encoding a repressor protein, wherein when the repressor protein is expressed it represses the repressible promoter and thus it represses the expression of the site specific recombinase.[1] Applicant contemplates to use RNA silencing against the mRNA encoding the repressor protein to induce the repressible promoter to direct expression of the site specific recombinase in the cell, which site specific recombinase excises the preselected DNA from the cell genome.[2] However, as noted in the non-final Office action of 02/13/2006, based on the teachings of the art, one of skill in the art would not readily recognize that silencing of a single repressor protein would necessarily result in the de-repression of the cognate promoter.[3] The art clearly teaches that transcription is carried out by assemblies of transcription factors, and many of them are redundant in the cell.[4] For example, Arnold et al. (IntJ Dev Biol, 1966, 40: 345-353, Abstract, of record) studying the role of the four myogenic regulating genes during mouse embryogenesis have found that Myf-5 and MyoD individually are not essential for the skeletal muscle development because they have redundant function.[5] The specification does not provide any example of a repressible promoter/repressor protein pair that could be used in the present invention.[6] The art does not provide this guidance.[7] Therefore, one of skill in the art would not know what promoter/repressor pair to chose [sic] among the many existing possibilities.[8] To practice the claimed invention, one of skill in the art would have to first determine how the transcription machinery assembles to each specific promoter, the transcription factors that are part of that machinery, and which transcription factors are redundant.[9] It is noted that this is not routine experimentation.[10] It is also noted that the same promoter can be active in one cell type and inactive in another cell type, depending on what transcription factors assemble at the promoter in a particular cell type.[11] The data above is known only for a few promoters in a few cells, and therefore, one of skill in the art would require undue experimentation to accumulate the necessary knowledge to practice the invention with any promoter, in any cell (in vitro or in vivo) or organism.[12] Importantly, Applicant did not address this issue.[13]
>
> (Present Office Action, page 4, l. 6 to page 5, l. 14; superscripts added.)

For ease of reference, each of the sentences in the passage above is consecutively numbered as indicated by the superscript numeral following each sentence.

First, Applicant wishes to point out that the type of genetic circuit described by the Examiner as being required, but allegedly not being enabled (i.e., "the main problem;" see sentence no. 1 of passage) is the subject matter of U.S. Pat. No. 5,723,765

issued March 3, 1998 ("the '765 patent"), which is discussed in and *incorporated by reference* in the instant application. (See ¶81 on page 24 and ¶84 on page 26 of the originally filed specification.) Each of independent claims 1, 10, 20, 28, 37, 46 and 55 of the '795 patent recites modified plants or plant cells or method of making the same, wherein the plants/plant cells comprise DNA sequence for a repressible promoter operably linked to a gene of interest and encoding a repressor protein specific for the repressible promoter, without limitation. Moreover, the '795 patent further gives specific examples of repressor proteins and their systems that may be used, namely, Tn10 tet repressor and the lac operator repressor system. (See, e.g., claim 12 of the '795 patent at col. 37, l. 10-12.)

The Examiner is reminded that U.S. patents are presumed to be valid, and thus enabled, under 35 U.S.C. §282. Accordingly, U.S. Patent No. 5,723,765 demonstrates conclusively for plants, and is also strong evidence beyond plants, that the main aspect of the Examiner's rejection is incorrect, since this aspect was enabled even before the 1998 issue date of the '795 patent, namely at its 1995 priority date. (Specific evidence in support of enablement of animal embodiments is also provided hereinbelow.) In this regard, Applicant also wishes to point out that, as set forth in MPEP 2164.05(a), as time advances, so does the facility of enablement:

> The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date.

In addition, as described on page 24, l. 20-23 of the originally filed specification, U.S. Patent No. 6,242,667 issued June 5, 2001 to Bujard et al. from an application filed September 8, 1998, which is incorporated by reference in the instant application, also discloses and claims transgenic plants having promoter/repressor pairs that may be used in implementing the presently claims invention.

Accordingly, even on these bases alone, the present rejections for lack of enablement, especially as regarding plants/plant cells, should be withdrawn.

Second, with respect to enablement of human and animal cells and transgenic animals, the '667 patent to Bujard (again, discussed on page 24, l. 20-23 and incorporated by reference in the instant application), specifically teaches repressible promoter/repressor pairs that may used to implement the presently claimed invention and provides actual examples, not only of cells, but of transgenic mice incorporating the promoter/repressor pair constructs. (See U.S. Pat. No. 6,242,667, col. 52, l. 31 to col. 54, l. 39.) Moreover, although the claims of the '667 patent itself are directed to transgenic plants, Applicant wishes to point out that its parent application filed June 7, 1995 issued as U.S. Patent No. 5,912,411 on June 15, 1999, which is statutorily presumed valid and which is of record, specifically *claims* transgenic mouse embodiments including the repressible promoter/repressor pairs. Thus, explicit and unambiguous support for enablement of animal/human cell and transgenic animal embodiments of the presently claimed invention with respect to the Examiner's alleged "main problem" is found in the prior art and in the originally filed specification.

Third, and further to the above, the Examiner's assertions in sentence nos. 6 through 8 of the cited passage of the present Office Action that the specification fails to provide any example of a repressible promoter/repressor pair that could be used (sentence 6), that the prior art fails to provide this guidance (sentence 7) and thus one skilled in the art would not know which repressible promoters/repressor pairs to use (sentence 8) are plainly erroneous. Instead, all of the information that the Examiner has asserted is lacking *is* explicitly recited, including with reference to both supporting patents and non-patent literature documents that are expressly incorporated by reference, at ¶¶80 and 81 on pages 23 and 24 of the originally filed specification, excerpts of which are reprinted below.

> [00080] The repressor protein coded by the repressor mRNA transcript may be an inhibitory transcription factor capable of directly interacting with the regulatory sequences of the repressed gene, whether endogenous or engineered, as known in the art or may indirectly interact with other biomolecules present in the cell to repress the repressed gene. For example, for plant embodiments of the invention, Tn10 tet repressor systems, as described in Gatz and Quail (1988) and Gatz, et al. (1992), can be adapted for use according to the invention. In this system, a modified Cauliflower Mosaic Virus (CaMV) 35S promoter containing one or more, e.g. three, tet operons is used; the Tn10 tet repressor gene produces a repressor protein that binds to the tet operon(s) and prevents the expression of the

gene to which the promoter is linked. The presence of tetracycline inhibits binding of the Tn10 tet repressor to the tet operon(s), allowing free expression of the linked gene. Gatz and Quail, "Tn10-encoded tet repressor can regulate an operator-containing plant promoter," Proc. Natl. Acad. Sci. USA, 85:1394-1397 (1988) and Gatz, et al., "Stringent repression and homogenous derepression by tetracycline of a modified CaMV 35S promoter in intact transgenic tobacco plants," The Plant Journal, 2:397-404 (1992), hereby incorporated by reference in their entireties. However, the present invention is not concerned with regulation of the system by tetracycline, although such regulation for which the prior system was designed may optionally be left intact according to the present invention.

Originally filed specification, page 23, l. 28 to page 24, l. 16.

[00081] Tetracycline responsive promoter systems known in the art for mammalian cells can similarly be adapted for use according to the invention. For example, US Patents 5,723,765 and 6,242,667 disclose suitable repressor systems, and are hereby incorporated by reference in their entireties.

Originally filed specification, page 24, l. 20-23.

Fourth, in sentence nos. 2-5 and 9-12 of the above cited passage of the present Office Action, the Examiner repeats a previously made argument alleging non-enablement on the basis that "one of skill in the art would not readily recognize that silencing of a single repressor would necessarily result in the de-repression of the cognate repressor..[and] [t]hat the art clearly teaches that transcription is carried out by assemblies of transcription factors, and many of them are redundant in the cell," etc. (See sentence nos. 2-5 and 9-12 in passage above for full arguments of Examiner.) In sentence no. 13, the Examiner asserted that "[i]mportantly, Applicant did not address this issue." (Emphasis added.)

This aspect of the present rejection is overcome for the following reasons.

Applicant first wishes to point out that the Examiner's assertion that Applicant did not address the referenced issue (regarding silencing a single repressor, etc.) is incorrect. The Examiner apparently inadvertently overlooked Section III(B.)(6) on page 17, l. 14 to page 18, l. 14 of the Amendment filed June 13, 2007 where Applicant addressed this specific issue. In addition, this particular aspect of the rejection was also responded to by submission, in the Information Disclosure Statement ("IDS") concomitantly filed with

Applicant's January 29, 2007 Amendment, of (i.) Applicant's Pre-Appeal Brief Request for Review including Applicant's Pre-Appeal Brief Arguments, filed October 31, 2006 in parent application ser. no. 10/354,903, the arguments of which are incorporated herein, and (ii.) Notice of Panel Decision from Pre-Appeal Brief Review [item (i.)] issued December 14, 2006 in parent application ser. no. 10/354,903. However, Applicant inadvertently failed to further discuss the relevance of these IDS submissions (to the present issue) in the January 29, 2007 Amendment and the Examiner apparently inadvertently failed to recognize their relevance while reviewing them. Accordingly, they are now discussed herein.

With reference to IDS submissions (i.) and (ii.) of the prior paragraph, Applicant wishes to point out that the Examiner rendered enablement rejections in parent application serial no. 10/354,903 on the same basis and citing the same support as that rendered in the instant application for the aspect of rejection (in sentence nos. 2-5 and 9-12). Applicant's Pre-Appeal Brief Request for Review in ser. no. 10/354,903 [Item (i.)], specifically addressed these issues in Section D. on pages 4 and 5 thereof, to which the Examiner is respectfully directed. The Notice of Panel Decision from Pre-Appeal Brief Review issued December 14, 2006 in ser. no. 10/354,903 [item (2.)], to which the Examiner is also specifically directed, specifically withdrew these rejections based on Applicant's arguments and observations. In other words, the same bases of rejection that the Examiner now uses were found to be unpersuasive by the Panel.

In addition, having shown above that specific examples of repressible promoter/repressor pairs are explicitly provided by the originally filed specification, both directly and by incorporation by reference of the referenced patents, and that U.S. Pat. No. 5,723,765 as discussed above properly places no limitations whatsoever of specific repressible promoters/repressors in various independent claims, Applicant again wishes to point that it is not the policy of the USPTO to limit claims to only those embodiments that have been worked or are preferred. As set forth in MPEP 2164.08:

> In In re Goffe, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976), the court stated:
>
> > [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found

> will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

The instant application directly discloses and discloses by incorporation by reference specific repressible promoter/repressor pairs that have been demonstrated to work, as shown by the examples of U.S. Patent Nos. and 5,723,765 and 6,242,667, and which can be used to implement the presently claimed invention. Just as claims of U.S. Pat. No. 5,723,765 were not limited to the specific repressible promoter/repressor pairs, the instant claims also should not be so-limited.

Even for the reasons discussed above alone in connection with the alleged "main problem," the present rejection for alleged lack of enablement should be withdrawn.

III(B.) The Examiner then asserted teachings of various previously cited non-patent literature references as allegedly compounding the alleged "main problem" with enablement, i.e. that discussed in Section II(A.) above, as follows.

> This is compounded by the teachings of Sledz et al., Opalinska et al., and the other references cited by the Examiner in the non-final Office action of 02/13/2006.[14] It is noted that Applicant's arguments regarding Woessmann et al. are found persuasive.[15] However, the teachings of Sledz et al. and Opalinska et al. are still applied as set forth in the non-final Office action of 02/13/2006.[16] Although the teachings of Sledz et al. do not apply to plants, beside plants and cells in culture, the claims are broadly drawn to any animal.[17] With respect to Opalinska et al., Applicant did not provide any evidence that their teachings cannot be also applied to siRNAs.[18] Applicant's arguments cannot replace evidence when evidence is necessary.[19] The argument that the antisense oligonucleotide and siRNAs act via entirely different mechanisms is not found persuasive because the citation from Opalinska et al. does not refer to this.[20] The citation refers to problems such as in vivo delivery to a cell, which has nothing to do with the mechanism of action, which comes into effect after the antisense oligonucleotides or siRNAs are delivered to the cell and reach their target inside the cell.[21] The art clearly teaches that the same problems apply to siRNAs (which are oligonucleotides), i.e., problems with the delivery to and inside a desired cell such that they reach their intracellular target.[22] Therefore, even if, in certain situation, silencing in animals can take place, this is still unpredictable (see Sledz et al. and Opalinska et al), which adds to the main problem discussed above.[23] For all these reasons, the rejection is maintained.[24]
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> (Present Office Action, page 5, l. 14 to page 6, l. 10; superscripts added.)

For ease of reference, each of the sentences in the passage above is consecutively numbered, continuing from the passage reprinted in Section II(A.), as indicated by the superscript numeral following each sentence.

III(B.)(1.) Plants

(a.) The Examiner has acknowledged that "gene silencing is well documented in plants." (Present Office Action, page 4, l. 6.) The Examiner has also acknowledged that Sledz (2005) does not apply to plants, but asserts that the claims are more broadly drawn, including animals (sentence no. 17 of OA passage above).

Applicant wishes to point out that the assertion that all claims are directed more broadly than plants is incorrect. Indeed, dependent claims 36-38 are all directed to, and limit their base claims to, plants or plant cells. Moreover, new dependent claims 39 and 40 added herein also limit their base claims to plants or plant cells.

(b.) With respect to Opalinska, it does not bear on enablement in plants as shown by Applicant's remarks and evidence presented at page 11, l. 6-21 of the Amendment filed January 29, 2007, to which the Examiner is respectfully directed. In brief, Applicant discussed references of record showing three different methods for obtaining efficient and consistent gene silencing in plants – which necessarily includes "delivery" -, and references of records documenting the intercellular spreading of silencing signals in plants. In addition, as pointed out at page 19, l. 13-16 of the Amendment filed January 29, 2007, the asserted application of Opalinska against enablement in plants also does not take into account the ability to express silencing RNAs within plants. Thus, the Examiner's assertion in sentence no. 18 of the OA passage above that Applicant did not provide any evidence that the teaching of Opalinska cannot also be applied to siRNA (here in plants) is both irrelevant to enablement in plants and, in any case, incorrect, since Applicant has demonstrated that the art cited by Applicant clearly and unambiguously supports enablement of RNA silencing of a gene in plants. As a matter of basic principles, it should also be pointed out that when there are multiple known ways of achieving the *same* aim, here RNA silencing of a gene, which is a step/part of the presently claim invention, it is easier to achieve that aim, not more difficult.

(c.) With respect to the Examiner's assertion in sentence no. 14 of the OA passage above, regarding compounding of the alleged main problem by "the other references cited by the Examiner in the non-final Office action of 02/13/2006," it appears that the Examiner is specifically referring to the references used by the Examiner to assert the alleged non-enablement of gene insertions required to make the cells/plants animals of the invention. In this regard, Applicant respectfully directs the Examiner attention to Section II(A.) on page 9 and 10 of the Amendment filed January 17, 2006, where Applicant specifically incorporated by reference and discussed Applicant's Pre-Appeal Brief Request for Review in parent application U.S. ser. no. 10/354,903 and The Notice of Panel Decision from Pre-Appeal Brief Review issued December 14, 2006 issued in response to the same. As previously pointed out by Applicant in the Amendment filed January 17, 2006, the same grounds of rejection now asserted (in connection with the enablement of the gene insertions) were made in the parent application but were found to be unpersuasive by the Panel. Accordingly, the Examiner is urged to consider the referenced papers of the parent application, which have previously been made of record herein, and withdraw the instant bases of rejection.

In view of the above, the Examiner is respectfully requested to withdraw the present rejection of claims directed to plants or plant cells, namely, claims 36-40.

III(B.)(2.) Animals

(a.) Animals - Sledz et al. (2005) and Opalinska (2002)

The Examiner has continued to assert Sledz et al. (2005) "as set forth in the non-final Office Action of 02/13/2006" (sentence no. 16 of OA passage above). The passage of Sledz originally cited for delivery concerns by the Examiner in the nonfinal Office Action mailed February 13, 2006 ("First Office Action"), specifically relates to alleged stability issues in circulation, i.e., in the circulation of *animals*: "[t]he use of RNAi for therapeutic purposes will depend on other factors as well…[a]lthough siRNAs are relatively stable in cell culture conditions, they require enhanced nuclease and thermodynamic stability when in circulation *in vivo*." (First Office Action, page 10, l. 17-19.)

Applicant subsequently remarked, in Section III(C)(1.) on pages 20 and 21 of the Amendment filed June 13, 2006 that the Examiner's reliance on Sledz was improper because while Sledz describes challenges posed to therapeutic use (i.) Applicant is not claiming a therapy and (ii.) additional non-specific effects are not an issue to enablement so long as the desired effect occurs.

The Examiner then asserted that Sledz et al. (2005; "Sledz") is nevertheless a proper basis in showing nonenablment of the presently claimed invention since, even though Sledz is predominantly directed to gene therapy applications of RNAi, "delivery concerns and non-specific effects still apply if the invention is practiced in a living organism" and the current claims encompass "in vitro, ex vivo or in vivo" situations." (Final Office Action mailed August 29, 2006, page 8, l. 3-10.)

The present basis of rejection is traversed for the following reasons.

First, the Examiner's rationale for rejection by which the subject claims are asserted to be non-enabled since they could conceivably encompass therapeutic applications and since (according to the Examiner) Sledz alleges problems that need to be overcome *for such therapeutic use* constitutes a plain legal error. As pointed out in MPEP 2107.03 under the heading "Safety and Efficacy Considerations" (emphasis in original):

> [w]hile an applicant may on occasion need to provide evidence to show that an invention will work as claimed, it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness. See In re Sichert, 566 F.2d 1154, 196 USPQ 209 (CCPA 1977); In re Hartop, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); In re Anthony, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); In re Watson, 517 F.2d 465, 186 USPQ 11 (CCPA 1975); In re Krimmel, 292 F.2d 948, 130 USPQ 215 (CCPA 1961); Ex parte Jovanovics, 211 USPQ 907 (Bd. Pat. App. & Inter. 1981).

The Examiner's bases of rejection drawn from Sledz are clearly directed to optimizations and conditions that are only required for the safety and efficacy of human therapeutic use – not for enablement of the presently recited claims as written. For example, with respect to Sledz's assertion cited by the Examiner that siRNAs require increased stability *in circulation* – there is no requirement in the claims that siRNAs (if such are used) are delivered via the circulation. Indeed, as most obviously apparent to those skilled in the art and as reflected in the prior art (see newly submitted Bertrand et al (2002) – also

discussed below), silencing RNAs can be directly/locally delivered to a target tissue by injection into a subject. Further, although it may be desirable, according to Sledz, for siRNA to have longer circulation half-life, it has no bearing on enablement – indeed, as with various drugs of short-half life, levels of drug could be maintained by continuous infusion (and therefore replenishment). Thus, it cannot be seen how the Examiner's alleged requirement for improved circulation performance bears on enablement of the presently claimed invention.

Similarly, with respect to non-specific effects, Applicant again wishes to point out that they bear no relationship to enablement as what is important to enablement is whether the desired effect occurs. Many drugs have side effects or off-target effects. Traditional cancer chemotherapy agents are harmful to normal cells but are more harmful to cancerous cells. In this regard, the Examiner again is improperly requiring a level of enablement that provides an optimized commercial product. Indeed, as set forth in MPEP 2164 (emphasis added):

> [T]o comply with 35 U.S.C. 112, first paragraph, it is not necessary to enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect.

If the Examiner is aware of a specific exception to this rule that applies to the instant subject matter, Applicant respectfully requests that the Examiner provides such details to Applicant.

Second, as Applicant previously pointed out, *in vivo* RNA silencing in animals was readily obtainable as shown for mice and *Drosophila* two preeminent model organisms – in the following previously and newly disclosed references:

1. Lewis et al. (2002), **Efficient delivery** of siRNA for inhibition of gene expression in postnatal mice, Nat. Genet. 32: 1107-1108 (of record);
2. Song et al. (2003) RNA interference targeting Fas protects mice from fulminant hepatitis, Nat. Med. 9: 347-351 (of record);
3. McCaffrey et al. (2002) RNA interference in adult mice, Nature 418: 38-39 (of record); and

4. Piccin et al. (2001) Efficient and heritable functional knock-out of an adult phenotype in Drosophila using a GAL4-driven hairpin RNA incorporating a heterologous spacer, Nuc. Acid Res. 29(12) e55 page 1-5 (of record).

5. Bertrand et al. (2002) Comparison of antisense oligonucleotides and siRNAs in cell culture and in vivo, Biochem & Biophy Res. Comm. (296) 1000-1004 (*newly submitted*).

6. McCaffrey et al. (2003) Inhibition of hepatitis B virus in mice by RNA interference, Nat Biotechnol. 2003 Jun; 21(6):639-44. Epub 2003 May 12 *(newly submitted* – Abstract Only).

7. Zender et al. (2003) Caspase 8 small interfering RNA prevents acute liver failure in mice, Proc Natl Acad Sci U S A. 2003 Jun 24;100(13):7797-802. Epub 2003 Jun 16 (*newly submitted*).

8. Filleur et al. (2003) SiRNA-mediated inhibition of vascular endothelial growth factor severely limits tumor resistance to antiangiogenic thrombospondin-1 and slows tumor vascularization and growth, Cancer Res. 2003 Jul 15 63(14):3919-22 (*newly submitted*).

9. Reich et al. (2003) Small interfering RNA (siRNA) targeting VEGF effectively inhibits ocular neovascularization in a mouse model, Mol Vis. 2003 May 30;9:210-6 (*newly submitted*).

The Examiner has asserted (in sentence no. 23 of the OA passage above) that "even if in certain situations, silencing in animals can take place this is still unpredictable." The Examiner's apparent position that the unpredictability is so great as to prevent enablement in animals is not supported by the submitted evidence. Indeed, what is pertinent about listed references 1-3 above is that no unusual or special preparation of siRNA was required to achieve silencing in mice; silencing was readily obtained using hydrodynamic (high pressure) injection *in vivo*. Listed references 1-3 are not "certain circumstances" that cannot be repeated – they are a guide to readily achieving siRNA delivery and RNA silencing in animals. Similarly, RNAi silencing was also readily achieved in the other references listed

above as well. Contrary to what would be expected based on the Examiner's assertions based on Sledz and Opalinska, silencing was conclusively and readily obtainable by the methods of the above listed articles.

Further, even Woessmann et al. (2003), which the Examiner previously cited as a basis of rejection, teaches that "effective siRNA are usually identified at high frequency not only for analyzing cultured cells but also for the induction of RNAi in mice." (Woessmann et al. (2003), page 274, right-column, l. 18-21; citing documents 1 through 3 listed above; emphases added.)

Of note, Bertrand et al. (2002), i.e., article no. 5 listed above, teaches that silencing of a reporter gene can be readily obtained *in vivo* in a xenograft tumor model in mice by injecting siRNAs directly into the target with a commercially available dendrimer carrier, Cytofectin GSV. (See Abstract and whole document.) In addition, in contrast to the Examiner's assertions, Bertrand et al. conclude that:

> The preliminary results mean that siRNA are promising tools to specifically inhibit the gene expression in vivo for three reasons:
> (1) They are powerful agents in cell culture.
> (2) It seems that no major hurdle prevents them from being efficient in vivo.
> (3) They are fairly resistant to biodegradation in serum, which is compatible with future use as a new type of gene expression targeting drug.
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> (Bertand et al. (2002) page 1004, R-column, l, 8-15.)

Third, the Examiner's assertion in sentence no. 22 of the OA passage above that "[t]he art [presumably Opalinska] clearly teaches that the same problems apply to siRNAs (which are oligonucleotides), i.e., problems with the delivery to and inside a desired cell such that they reach their intracellular target" is not accurate. As application previously set forth in the Amendment filed January 29 2007, the statements in Opalinska and all of their underlying support regarding alleged delivery problems are directed to conventional DNA-based oligonucleotides, not RNAs. The Examiner' rejection is based on an inference that RNA oligonucleotides, i.e., polyribonucleotides, will behave as DNAs, i.e., polydeoxyribonucleotides. Nowhere is the inference even made in the cited references. Thus, the references do not teach what the Examiner has asserted.

In contrast to the inference asserted against the present claims, Applicant has provided evidence from the art that supports enablement and that is specific to silencing

RNAs. Weighed against a more-remote inference from a less relevant reference, the on-point evidence of multiple references presented by Applicant should prevail in showing enablement.

Fourth, while the Examiner has (incorrectly) asserted that Opalinska is an authoritative reference as to delivery of oligonucleotide therapeutics (and siRNAs as inferred by the Examiner), Applicants wishes to point out Opalinska's glaring omission of electroporation-based oligonucleotide delivery methods known in the art, for both in vitro and in vivo applications. Thus, in addition to the references discussed above, the following electroporation references (disclosed in accompanying IDS) also make it clear that oligonucleotides, including siRNAs, could be readily delivered into desired cells and tissues, in vitro and in vivo:

10. Baba et al. (2000) In vivo electroporetic transfer of bcl-2 antisense oligonucleotide inhibits the development of hepatocellular carcinoma in rats, .Int. J. Cancer. 2000 Jan 15; 85(2):260-6 (*newly submitted* – Abstract Only).

11. Liu et al. (2001) Improved intracellular delivery of oligonucleotides by square wave electroporation, Antisense Nucleic Acid Drug Dev. 2001 Feb; 11(1):7-14 (*newly submitted* – Abstract Only).

12. Nunamaker et al. (2003) Electroporation-mediated delivery of catalytic oligodeoxynucleotides for manipulation of vascular gene expression, Am J Physiol Heart Circ Physiol. 2003 Nov; 285(5):H2240-7. Epub 2003 Jul 24. (*newly submitted* – Abstract Only).

13. Trezise et al (2003) In vivo gene expression: DNA electrotransfer, Curr Opin Mol Ther. 2003 Aug; 5(4):397-404 (*newly submitted* – Abstract Only).

14. Kishida et al. (2003) Sequence-specific gene silencing in murine muscle induced by electroporation-mediated transfer of short interfering RNA, J Gene Med. 2004 Jan; 6(1):105-10 Published online 12 Sep 2003 (*newly submitted* – Abstract Only).

In view of the above, it is clear that electroporation was yet another technique available to and enabling the skilled worker to readily deliver oligonucleotides into cells, both in vitro and in vivo.

As set forth in MPEP 2164.05, "the determination [of enablement] should always be based on the weight of all the evidence." As set forth in MPEP 2164.08, "the scope of enablement must only bear a 'reasonable correlation' to the scope of the claims."

Applicant has addressed each and every aspect of the Examiner's asserted case for non-enablement by showing that the cited references were improperly relied upon by the Examiner, that improper standards for enablement have been applied, and/or by showing enablement of the specific aspects of the invention with reference to the evidence previously and now made of record. In view of Applicant's arguments and the evidence discussed above, the weight of the evidence supports a finding of enablement of the presently examined claims.

For all of the reasons stated hereinabove, Applicant respectfully requests withdrawal of the present rejection of the claims for alleged lack of enablement under 35 U.S.C. 112, first paragraph.

IV. Claim rejections under 35 U.S.C. §101

Claims 18, 19, 22, 24, 29, 30 and 32 are presently rejected under 35 U.S.C. §101 as allegedly being directed to non-statutory subject matter since (1.) "the term 'cell not integrated with a human being' is allegedly not defined by the specification" and is asserted to be new matter and (2.) even so, further allegedly because the cells "could be present in a human being and not integrated" or "transplanted into a human being and not become integrated with the human being (i.e. transplanted blood cells, for example') but, according to the Examiner would still be part of a human being and therefore improperly encompass a human being. (Present Office Action, ¶¶5 and 6.)

Claims 18-20, 22, 29, 30 and 32 were originally rejected under 35 U.S.C. §101 as allegedly encompassing a human being in the Office Action mailed February 16, 2006 (see ¶¶ 2 and 3 thereof). Specifically, the Examiner asserted therein that "[t]he term 'cell' is not defined by the specification…[i]n the absence of the contrary, the cell is present or intended to be present in a human being and therefore being an inseparable part of the human itself." Id. In response to said rejection, independent "cell" claims 18

and 29 were amended to recite the limitation "not integrated with a human being" and "multi-cellular organism" claim 20 was amended to recite the limitation "non-human," by the Amendment filed June 13, 2006. In response, the 35 U.S.C. §101 rejections were withdrawn in the Final Office Action mailed August 29, 2006 (see ¶3 thereof). The rejection is now reinstated with respect to the claims that recite cells (rather than non-human multi-cellular organisms).

The present rejection of the claims is overcome for the following reasons.

First, with respect to the new matter rejection of the claims, the objected to language "not integrated with a human being" has been deleted from independent claims 18 and 29. Therefore, the asserted "new matter" basis of the rejection is no longer applicable.

Second, the official policy of the United States Patent and Trademark Office ("USPTO") with respect to claims being directed to human beings or including such within their scope is set forth as follows:

> A claim directed to or including within its scope a human being will not be considered patentable subject matter under 35 U.S.C. 101.
>
> "Notice: Animals--Patentability," 1077 Official Gazette U.S. Pat. and Trademark Off. 8 (April 21, 1987)

Presently rejected claims 18, 19, 22, 24, 29, 30 and 32 directly or indirectly recite "[a] cell" and, thus, although not directed to a human being nevertheless, according to the Examiner, include a human being within their scope. As discussed during the Examiner Interview of June 5, 2007, an explicit disclaimer of whatever scope of claims 18, 19, 22, 24, 29, 30 and 32 includes a human being should be responsive to the present rejection without raising any new matter issues.

Accordingly, Applicant hereby explicitly disclaims whatever scope of claims 18, 19, 22, 24, 29, 30 and 32 include a human being.

In view of the above, withdrawal of the present rejection of the claims under 35 U.S.C. §101 is hereby requested.

V. Conclusion

Claims 1-40 are pending. Claims 1-16 are presently withdrawn as a result of being deemed to be directed to a non-elected inventions and claims 21, 23, 26, 28, 31 and 33-35 are presently withdrawn as being drawn to non-elected species.

Pursuant to this paper, Applicant submits that elected claims 17-20, 22, 24, 25, 27, 29, 30, 32 and 36-40 (reading on the elected invention) are in condition for further examination and allowance, which action is hereby requested. Upon a finding of allowance for any of the elected claims, Applicant requests rejoinder and allowance of any presently withdrawn claim that is dependent on an allowed elected claim.

If upon considering this paper, the Examiner still considers any claim to be unallowable, Applicant respectfully requests that the Examiner telephone Applicant at the number below to discuss any issues that are considered to remain.

Date: July 15, 2007

Respectfully submitted,

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Enclosure

IDS – substitute for Form PTO-1449